ICDDR,B: Centre for Health & Population Research: RRC APPLICATION FORM

RESEARCH PROTOCOL

2000-012

FOR OFFICE USE ONLY

Protocol No: Date received:

RRCApproval: Yes/ No Date:

ERC Approval: Yes/No Date:

Project Title: Use of metronidazole in improving nutritional rehabilitation of severely malnourished children recovering from diarrhea: a randomized controlled trial

Theme and key words: Severe malnutrition, nutritional rehabilitation, metronidazole treatment

Principal Investigator: Dr. Tahmeed Ahmed **Division:** CSD **Phone:** 2304

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Co-Principal Investigator(s): Prof. George J. Fuchs

Co-Investigator(s): Dr. Ali Miraj Khan, Dr. Md. Jahangir Hossain, Dr. Md. Munirul Islam, Dr. Baitun Nahar

Student Investigator/Intern: None

Collaborating Institute(s): None

Population: Inclusion of special groups *(Check all that apply)*:

Gender
- ☑ Male
- ☑ Females

Age
- ☑ 0 – 5 years
- ☐ 5 – 9 years
- ☐ 10 – 19 years
- ☐ 20 +
- ☐ > 65

- ☐ Pregnant Women
- ☐ Fetuses
- ☐ Prisoners
- ☐ Destitutes
- ☐ Service providers
- ☐ Cognitively Impaired
  - ☐ CSW
- ☐ Others (specify) _____

Project / study Site *(Check all the apply)*:
- ☑ Dhaka Hospital
- ☐ Matlab Hospital
- ☐ Matlab DSS area
- ☐ Matlab non-DSS area
- ☐ Mirzapur
- ☐ Dhaka Community
- ☐ Chakaria
- ☐ Abhoynagar
- ☐ Mirsarai
- ☐ Patyia
- ☐ Other areas in Bangladesh _____
- ☐ Outside Bangladesh
  name of country: _____
- ☐ Multi centre trial
  (Name other countries involved)

_____

Type of Study *(Check all that apply)*:
- ☐ Case Control study
- ☐ Community based trial / intervention
- ☐ Program Project (Umbrella)
- ☐ Secondary Data Analysis
- ☑ Clinical Trial (Hospital/Clinic)
- ☐ Family follow-up study
- ☐ Cross sectional survey
- ☐ Longitudinal Study (cohort or follow-up)
- ☐ Record Review
- ☐ Prophylactic trial
- ☐ Surveillance / monitoring
- ☐ Others

Targeted Population *(Check all that apply)*:

- ☑ No ethnic selection (Bangladeshi)
- ☐ Bangalee
- ☐ Tribal groups
- ☐ Expatriates
- ☐ Immigrants
- ☐ Refugee

Consent Process *(Check all that apply)*:

- ☑ Written
- ☐ Oral
- ☐ None
- ☑ Bengali language
- ☐ English language

Proposed Sample size: Total sample size: 140 children_____☐

Sub-group: Metronidazole, 70 children_____☐

Sub-group: Placebo, 70 children_____☐

Determination of Risk: Does the Research Involve *(Check all that apply)*:

- ☐ Human exposure to radioactive agents?
- ☐ Fetal tissue or abortus?
- ☐ Investigational new device?
  (specify)_____
- ☐ Existing data available from Co-investigator
- ☐ Human exposure to infectious agents?
- ☐ Investigational new drug
- ☐ Existing data available via public archives/source
- ☐ Pathological or diagnostic clinical specimen only
- ☐ Observation of public behavior
- ☑ New treatment regime

Yes/No

☑ ☐ Is the information recorded in such a manner that subjects can be identified from information provided directly or through identifiers linked to the subjects?

☐ ☑ Does the research deal with sensitive aspects of the subject's behavior; sexual behavior, alcohol use or illegal conduct such as drug use?

Could the information recorded about the individual if it became known outside of the research:

☐ ☑ a. place the subject at risk of criminal or civil liability?

☐ ☑ b. damage the subject's financial standing, reputation or employability; social rejection, lead to stigma, divorce etc.

Do you consider this research *(Check one)*:

- ☐ greater than minimal risk
- ☑ no risk
- ☐ no more than minimal risk
- ☐ only part of the diagnostic test

Minimal Risk is "a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as a part of routine physical examination".

Yes/No

☐ ☐ Is the proposal funded?

If yes, sponsor Name: World Bank, ICDDR,B Nutrition Centre

Is the proposal being submitted for funding ?

☐ ☐ If yes, name of funding agency: Not applicable

Do any of the participating investigators and/or their immediate families have an equity relationship (e.g. stockholder) with the sponsor of the project or manufacturer and/or owner of the test product or device to be studied or serve as a consultant to any of the above? No

IF YES, submit a written statement of disclosure to the Director.

Dates of Proposed Period of Support	**Cost Required for the Budget Period ($)**			
(Day, Month, Year - DD/MM/YY)	*a. Ist Year*	*2nd Year*	*rd Year*	*Other years*
Beginning date: 01.10.2000	*21,519*	*25,690*	_____	_____
End date: 30.09.2002	*b. Direct Cost :$47,209*		*Total Cost :* _____	

Approval of the Project by the Division Director of the Applicant

The above-mentioned project has been discussed and reviewed at the Division level as well by the external reviewers. The protocol has been revised according to the reviewer's comments and is approved.

Dr. M. A. Salam
Name of the Division Director
(Acting)

_____ Signature

04-7-2000
Date of Approval

Certification by the Principal Investigator

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

Signature of PI Tahmeed Ahmed

Date: 04.07.00

Name of Contact Person (if applicable)

Table of Contents

[X] Check here if appendix is included

PROJECT SUMMARY: Describe in concise terms, the hypothesis, objectives, and the relevant background of the project. Describe concisely the experimental design and research methods for achieving the objectives. This description will serve as a succinct and precise and accurate description of the proposed research is required. This summary must be understandable and interpretable when removed from the main application. **(TYPE TEXT WITHIN THE SPACE PROVIDED).**

Principal Investigator: Dr. Tahmeed Ahmed

Project Name: **Use of metronidazole in improving nutritional rehabilitation of severely malnourished children recovering from diarrhea: a randomized controlled trial**

Total Budget (Direct cost): $ 47,209 Beginning Date: 01.10.2000 Ending Date: 30.9.2002

A randomized double-blind trial has been designed to evaluate the efficacy of metronidazole in improving nutritional rehabilitation of severely malnourished children recovering from diarrhea by treating small intestinal anaerobic infection. Severely malnourished children of either sex (weight-for-length z-score <–3 according to the US National Centre for Health Statistics reference, or with edema), aged 6-60 months, with diarrhea and other associated illnesses including pneumonia will be enrolled into the study. Seventy eligible children will be randomized to receive metronidazole, and 70 to receive a placebo. The randomization will be stratified so that an equal proportion of children with edema are enrolled into each of the two groups. The children will be treated in the in-patient facility of the Clinical Research and Service Centre of the ICDDR,B according to routinely used standardized protocols for the acute and the nutritional rehabilitation phases of management. In addition, they will receive either metronidazole 30 mg/kg per day q8 hourly orally, or a placebo, for 7 days. All mothers will receive health and nutrition education, and hands-on training on preparation of nutritious diets from locally available, inexpensive foods. The metronidazole and placebo groups will be compared in terms of anthropometric indices on admission and upon discharge, rate of weight gain, and time to recovery (achieving weight-for-length z-score >–2). The variables will be compared within (if applicable) and between groups from enrollment to discharge. If metronidazole treatment (which is inexpensive) along with nutritional therapy is found to increase weight gain and reduce the period of stay in the NRU, then it will be possible to reduce the cost of treating severely malnourished children.

KEY PERSONNEL (List names of all investigators including PI and their respective specialties)

Name		Professional discipline/ specialty	Role in the project
1.	Dr. Tahmeed Ahmed	Pediatrician and Nutritionist	PI
2.	Prof. George J. Fuchs	Pediatric Gastroenterologist & Nutritionist	Co-PI
3.	Dr. Ali Miraj Khan	Internist	Co-Investigator
4.	Dr. Md. Jahangir Hossain	Internist	Co-Investigator
4.	Dr. Md. Munirul Islam	Internist	Co-Investigator
5.	Dr. Baitun Nahar	Internist	Co-Investigator

DESCRIPTION OF THE RESEARCH PROJECT

Hypothesis to be tested:

Concisely list in order, in the space provided, the hypothesis to be tested and the Specific Aims of the proposed study. Provide the scientific basis of the hypothesis, critically examining the observations leading to the formulation of the hypothesis.

1. Severely malnourished children have colonisation of the small intestine with anaerobic and aerobic bacteria. Treatment of intestinal anaerobic infection with metronidazole increases rate of weight gain of severely malnourished children recovering from diarrhea and other acute illnesses including pneumonia.

2. The treatment shortens the period of hospitalization for nutritional rehabilitation.

3. The treatment also reduces morbidity, including sepsis, during nutritional rehabilitation.

Specific Aims:

Describe the specific aims of the proposed study. State the specific parameters, biological functions/ rates/ processes that will be assessed by specific methods **(TYPE WITHIN LIMITS).**

This will be a prospective, double-blind, placebo-controlled randomized trial that will evaluate the efficacy of metronidazole in severely malnourished children admitted to the hospital with acute illness(es) including diarrhea and pneumonia/sepsis. The two major outcome variables that will be compared between the study and placebo groups are:

1. Rate of weight gain, calculated from lowest and discharge weights in terms of g/kg body weight per day
2. Days to achieve edema-free weight-for-length (WL) z-score >–2 according to the US National Centre for Health Statistics reference

Background of the Project including Preliminary Observations

Describe the relevant background of the proposed study. Discuss the previous related works on the subject by citing specific references. Describe logically how the present hypothesis is supported by the relevant background observations including any preliminary results that may be available. Critically analyze available knowledge in the field of the proposed study and discuss the questions and gaps in the knowledge that need to be fulfilled to achieve the proposed goals. Provide scientific validity of the hypothesis on the basis of background information. If there is no sufficient information on the subject, indicate the need to develop new knowledge. Also include the **significance and rationale** of the proposed work by specifically discussing how these accomplishments will bring benefit to human health in relation to biomedical, social, and environmental perspectives. **(DO NOT EXCEED 5 PAGES, USE CONTINUATION SHEETS).**

Background

Although knowledge about the pathophysiology and treatment requirements of the severely malnourished child has improved considerably, a review of data worldwide reveals that the median mortality rate has remained virtually unchanged at 20-30% for the past five decades (1). Even in the 1990s, mortality rates as high as 60% have been reported for hospitalized children with edematous malnutrition (1). The extremely high death rates have been attributed to faulty case-management. Research done earlier at the ICDDR,B showed that if severely malnourished children are discharged from hospital after treatment for diarrhea, they have a 14 times greater risk of death than their nutritionally better-off peers (2). These data emphasize the need for proper management of the acutely ill severely malnourished child during the episode of diarrhea and any other acute illness, and also optimum nutritional rehabilitation while the child recovers from the acute illness.

The current management of severely malnourished children is largely dependent on nutritional rehabilitation centre-based care where, most often, children are brought for acute medical problems including localized or systemic infections, dehydration and metabolic derangements. We have recently developed standardized protocols for both the acute as well as the nutritional rehabilitation phases of management of children with severe malnutrition and diarrhea. Implementation of the protocols resulted in a 47% reduction in mortality during the acute phase of management (3), and a 40% increase in weight gain during the nutritional rehabilitation phase as compared to conventional treatment (4). Key features of the protocol for the acute phase management include: slower rehydration with emphasis on oral rehydration, immediate feeding using defined dietary regimens consisting of local inexpensive foods, routine micronutrient supplementation and broad-spectrum antibiotic therapy, and expedient treatment of complications. The protocol for the nutritional rehabilitation phase is based upon the provision of diets that are inexpensive, locally available and culturally acceptable, so that the mothers can continue feeding the diets to the children after discharge from the nutritional rehabilitation unit (NRU). Unfortunately, space and staff constraints, which are universal problems, limit the number of children who can be accommodated in the NRU. Increasing the velocity of weight gain could result in a shortened period of stay in the NRU. A shorter period of stay in the NRU, where the mothers are also provided health and nutrition education, would enable further management of malnutrition at home, reduce the risk of nosocomial infection, and be cost-effective (5).

Ingestion of contaminated gruels by children living in unhygienic conditions that prevail in developing countries has been indicated to be a factor contributing to the diarrhea-malnutrition cycle (6). The upper small intestine of healthy subjects does not contain anaerobic bacteroides. Malnourished children have their upper small intestine colonised with microbes including aerobic and anaerobic bacteria (7,8). Omoike et al could culture the anaerobes Bacteroides and Clostridia from the duodenal aspirates of 15 out of 30 malnourished Nigerian children, compared to only one out of 22 well-nourished children (8). Bacterial colonisation of the upper small intestine is found with increased frequency in children with repeated episodes of diarrhea, which is commonly observed in severely malnourished children (9). This condition results in malabsorption of nutrients and has been suggested to be related to impaired growth in malnourished children (10). The qualitative and quantitative changes in upper intestinal flora in these circumstances alter the nutritional status of the human host (11). The colonising bacteria compete with the host for the ingested nutrients. There occurs a spectrum of clinical problems resulting from intraluminal bacterial catabolism of nutrients, often with the production of toxic metabolites, and injury to the small intestinal cells (12). Most patients with clinically significant malabsorption secondary to bacterial overgrowth have an intestinal flora that is largely overgrown with anaerobes (11). This overgrowth of bacteria is quite often asymptomatic in severely malnourished children (13) due to the blunted inflammatory response as a consequence of malnutrition (14,15). Rowland and McCollum, in a study on malnourished Gambian children,

showed a relationship between an upper small intestine contaminated with bacteria and the presence of parasites and abnormal jejunal salts (16). They concluded that until the cycle of upper small intestine colonisation and diarrhea is disrupted, a diet-based nutritional rehabilitation program could not be expected to be effective.

Although the use of broad-spectrum antibiotics including cotrimoxazole, or ampicillin and gentamicin in the initial management of the severely malnourished child is now accepted as a standard practice (17,18), these antibiotics while being effective against aerobic bacteria are ineffective against anaerobic gut flora. Metronidazole, an antimicrobial agent for the treatment of anaerobic infection, was found to be beneficial in resolving the signs of intestinal anaerobic infection including weight loss, anorexia and diarrhea in moderately malnourished children (19). Its effectiveness against mixed anaerobic and aerobic infections has also been reported (20,21). A clinical trial on malnourished children in Kingston, Jamaica in 1985-86 showed that treatment with metronidazole resulted in improved growth compared to controls, just as did a high energy nutritional intervention, but that the greatest and longest-lasting improvement was for children who received both interventions (22). This trial was performed on children with mild to moderate malnutrition and without any acute infection. The efficacy of metronidazole, however, has not been established by clinical trials in acutely ill severely malnourished children (23). Despite lack of convincing data, the use of metronidazole in the management of severely malnourished children is being advocated by certain experts (17).

Metronidazole has a spectrum limited to anaerobic bacteria and parasites including *Entamoeba histolytica* and *Giardia lamblia*. It is one of the most commonly used (or misused) over-the-counter medicine for diarrhea in Bangladesh (24). Short courses of metronidazole are well accepted by young children. Serious adverse reactions to the drug are rare (25). Gastrointestinal side effects such as nausea and metallic taste are frequent but rarely necessitate discontinuation of therapy. A disulfiram-like reaction can occur if ethanol is ingested concurrently, a circumstance which does not apply to young children.

Rationale

Severely malnourished children have symptomatic or subclinical of the small intestine with anaerobic bacteria, which causes malabsorption of nutrients and leads to impaired growth. Treatment with metronidazole in addition to routine nutritional rehabilitation will cure the anaerobic infection and, therefore, result in improved weight gain and shortened period of time for nutritional rehabilitation. This will ultimately result in reduced costs for the management of severely malnourished children recovering from diarrhea and other acute illnesses including pneumonia.

Significance

If metronidazole treatment (which is relatively inexpensive) along with nutritional therapy is found to increase weight gain and reduce the period of stay in the NRU, then it will be possible to rehabilitate a larger number of severely malnourished children without additional resources. This will also result in more mothers receiving health and nutrition education, who will subsequently act as peer educators in the community. Reduced morbidity as a result of metronidazole treatment will also decrease the overall cost of treatment. An increased weight gain at the beginning of nutritional rehabilitation will promote and strengthen further management at home. If found to be effective, metronidazole treatment will be incorporated into the standard case-management protocol for severely malnourished children.

Research Design and Methods

Describe in detail the methods and procedures that will be used to accomplish the objectives and specific aims of the project. Discuss the alternative methods that are available and justify the use of the method proposed in the study. Justify the scientific validity of the methodological approach (biomedical, social, or environmental) as an investigation tool to achieve the specific aims. Discuss the limitations and difficulties of the proposed procedures and sufficiently justify the use of them. Discuss the ethical issues related to biomedical and social research for employing special procedures, such as invasive procedures in sick children, use of isotopes or any other hazardous materials, or social questionnaires relating to individual privacy. Point out safety procedures to be observed for protection of individuals during any situations or materials that may be injurious to human health. The methodology section should be sufficiently descriptive to allow the reviewers to make valid and unambiguous assessment of the project. **(DO NOT EXCEED TEN PAGES, USE CONTINUATION SHEETS).**

Design

This will be a randomized, double-blind, placebo-controlled trial stratified by type of malnutrition (edematous or non-edematous). Eligible children will be assigned to one of the two treatment groups according to the random numbers table, using permuted blocks of variable lengths. In order to ensure equal distribution of edematous and non-edematous children in the two treatment groups, separate tables of random numbers will be used. A trained and responsible person not involved with the study will prepare the randomization lists and preserve the master code. The study drug and the placebo, in identical amber-colored bottles, will be procured from a pharmaceutical industry experienced in the preparation of drugs for clinical trials. The placebo will be made similar in colour to the study drug. The bottles will be stored in and dispensed from the hospital pharmacy.

Methods

Severely malnourished children of either sex (weight-for-length z-score <–3 or with edema), aged 6-60 months, with diarrhea and other associated illnesses including pneumonia will be enrolled into the study upon informed consent from the parents or guardians. The children will be treated in the in-patient facility of the Clinical Research and Service Centre of the ICDDR,B according to routinely used standardized protocols for the acute and the nutritional rehabilitation phases of management (3, 4). In addition, the children will receive either metronidazole 30 mg/kg per day q8 hourly orally, or a placebo, for 7 days. All mothers will receive health and nutrition education, and hands-on training on preparation of nutritious diet from locally available, inexpensive foods. Children not previously immunized will be vaccinated against the six communicable diseases under the national Expanded Program on Immunization (tuberculosis, diphtheria, pertussis, poliomyelitis, tetanus, and measles).

Exclusion criteria will include the following:

- Septicemic shock on admission (a combination of non-countable or low-volume radial pulse with no signs of dehydration, hypo- or hyperthermia, obtundation, hypoglycemia)
- Jaundice
- Hemolytic-uremic syndrome (a child with invasive diarrhea having the following features: a hematocrit of <20% or a drop in hematocrit by >10%, evidence of hemolysis ie., red blood cell fragmentation of >0.5%, serum creatinine >180 micromol/litre, a platelet count of <100,000 per cubic millimetre)
- Renal failure (a combination of oliguria or anuria in the absence of dehydration, hypertension, serum creatinine >180 micromol/litre, hyperkalemia)
- Any condition that would necessitate metronidazole therapy, i.e., giardiasis, amebiasis
- Children with pneumonia on treatment with chloramphenicol, an antibiotic that also affects anaerobic flora.
- Acute abdomen (intestinal obstruction, toxic colitis, or ileus due to intra-abdominal sepsis characterised by tender distended abdomen, absent bowel sounds, X-ray features of obstruction or toxic colitis; intestinal perforation characterised by tender abdomen, obliteration of liver dullness over the right costal margin, X-ray features of perforation of a hollow viscus)
- Children on an exclusion diet for the treatment of persistent diarrhea
- Tuberculosis (diagnosed on the basis of the modified Kenneth-Jones Criteria)
- Trisomy-21, cerebral palsy, or congenital organ defects (diagnosed on the basis of clinical history and physical examination)

Standardized protocol for management of severely malnourished children

Correction of dehydration

Dehydration is assessed by WHO criteria (26). Rehydration is accomplished over a more extended period of time than the usual 3-6 hours, avoiding intravenous (i.v.) fluids as far as possible. Some dehydration is managed with rice-ORS (Na^+, 90; K^+, 20; Cl^-, 80; citrate, 10 mmol/L; rice powder, 50 g/L), 10 mL/kg per hour for the first 2 hours, then 5 mL/kg/hour for next 10 hours or till the fluid deficit is corrected. Ongoing stool losses are replaced with ORS, 5-10 mL/kg after each watery stool. If a child is unable to drink due to weakness or vomiting, ORS is administered through a nasogastric (NG) tube.

In severe dehydration, initial hydration is accomplished with an intravenous fluid (Na^+, 133; K^+, 20; Cl^-, 98; acetate, 48 mmol/L; and 5% dextrose, *solution A*), 20 mL/kg in the first hour followed by 10 mL/kg in the second hour. ORS, 10 mL/kg/hour, is started at the end of first hour and continued as for the management of some dehydration.

When vomiting persists even after introducing an NG tube, 1/2 strength of solution A with additional K^+ and glucose yielding a concentration of 20 mmol K^+/L and 5% dextrose (*solution B*) is infused 10 ml/kg per hour for the first 2 hours, then 5 ml/kg per hour till correction of deficit or when the child can drink ORS.

Diet therapy

Feeding is begun immediately upon admission with a liquid diet, *milk suji* (appendix), given 2 hourly as per the following schedule:

Children with marasmus and marasmic kwashiorkor:

Day 1	10 ml/kg/feed (80 kcal/kg per day)
Day 2-3	12 ml/kg/feed (96 kcal/kg per day)
Day 4 onwards	If no diarrhea, 12 ml/kg/feed milk suji 100 (appendix) (144 kcal/kg per day)

Children with kwashiorkor:

Day 1-3	9 ml/kg/feed (72 kcal/kg per day)
Day 4 onwards	If no diarrhea, 9 ml/kg/feed milk suji 100 (108 kcal/kg per day)

Mothers are advised to breast-feed every half-hour if applicable. Anorexic children are fed with an NG tube. As soon as the acute phase is over, i.e., diarrhea has ceased, general condition is good, can take feeds orally, the children are transferred to the NRU. The diets used in the NRU are *khichuri, halwa* and milk suji which are inexpensive, culturally acceptable, rich in calories and can be easily prepared at home with locally available ingredients. Khichuri is made of rice, lentils, vegetables and oil (appendix). Energy and protein contents of 100 g cooked khichuri are 145 kcal and 3 g respectively. Halwa is made of wheat flour, lentils, molasses and oil, and 100 g of the cooked diet contains 240 kcal and 5 g of protein (appendix). Mothers who also stay with the children in the unit are given health and nutrition education. They prepare diets for the children under the supervision of a trained health worker, take care of, and feed their children. Since psychosocial stimulation is an important aspect of rehabilitation, mothers are encouraged to engage the children in playing with toys and listening to songs meant for children. There are two play times of one hour each in the morning and in the afternoon. As physical activity promotes growth during rehabilitation, limbs of the immobile child are passively moved by the mother. Mobile children are encouraged to do activities like walking, rolling on the mat, kicking or tossing a ball etc. After two weeks of nutritional rehabilitation, children >1 year of age are given the anti-helminthic, mebendazole, 100 mg two times daily for 3 days. The following feeding schedule is used in the NRU:

Diet	Item & amount	Energy intake Kcal/kg.day	Protein intake g/kg.day
1	Milk suji 10 ml/kg.feed (110ml/kg.day) 2 hrly (11 feeds per day) *	74	1.5
	Halwa 10 g/kg.feed 2 feeds per day	48	1.0
	Total	**122**	**2.5**
2	Milk suji 10 ml/kg.feed (110ml/kg.day) 2 hrly (11 feeds per day) *	74	1.5
	Halwa 10 g/kg.feed 2 feeds per day	48	1.0
	Khichuri 10 g/kg.feed 2 feeds per day	29	0.6
	Total	**151**	**3.1**
3	Milk suji 100 10 ml/kg.feed (110ml/kg.day) 2 hrly (11 feeds per day) *	110	2.8
	Halwa 10 g/kg.feed 2 feeds per day	48	1.0
	Khichuri 10 g/kg.feed 2 feeds per day	29	0.6
	Total	**187**	**4.4**
4	Milk suji 100 10 ml/kg.feed (110ml/kg.day) 2 hrly (11 feeds per day) *	110	2.8
	Halwa 10 g/kg.feed 3 feeds per day	72	1.5
	Khichuri 10 g/kg.feed 3 feeds per day	43	0.9
	Total	**225**	**5.2**
5	Milk suji 100 10 ml/kg.feed (40ml/kg.day) 6 hrly (4 feeds per day)	40	1.0
	Halwa 20 g/kg.feed 3 feeds per day	144	3.0
	Khichuri 20 g/kg.feed 3 feeds per day	87	1.8
	Total	**271**	**5.8**

* There is a gap in feeding at 4 a.m.

Diets 1, 2, 3 and 4 are provided on days 1, 2, 3 and 4 respectively of the nutritional rehabilitation phase. These diets ensure 2 hourly feeds with milk suji at least for the first 4-5 days of nutritional rehabilitation. Diet 5 is started only when the child achieves an intake of 225 kcal/kg per day, and is continued till the end of stay in the NRU. Most of the calorie and protein in diet 5 are derived from halwa and khichuri, the number of milk feeds being only four per day. Thereafter, halwa and khichuri can easily be continued at home. The child is given plain water in between the feeds. The amount of each feed offered and actually taken is recorded on a feeding chart.

Children are discharged from the NRU once they have achieved an energy intake of >250 kcal/kg per day (with 5 g/kg per day of protein intake), have attained a WL z-score >–2, are edema free, and have a good general condition.

Antibiotic therapy

In children without signs or symptoms of infection other than those of diarrhea, therapy is initiated with ampicillin 100 mg/kg per day q6 hourly and gentamicin 5 mg/kg per day q12 hourly i.m. or i.v. (17), and continued for 7 days. If no clinical or other evidence of septicemia is present after 48 hours, ampicillin is discontinued and

amoxycillin 100 mg/kg per day q8 hourly is given orally for 5 additional days. Children with pneumonia are treated with chloramphenicol 100 mg/kg per day q6 hourly i.v. for 24 hours and then orally for a total of 7 days (27). Children on treatment with chloramphenicol will not be enrolled because the antibiotic also affects anaerobic flora. Children with pneumonia being treated with ceftriaxone, which has no impact on anaerobic bacteria, will be enrolled subject to fulfilment of other conditions.

If septicemia is suspected, dose of ampicillin is increased to 200 mg/kg per day and continued with gentamicin for 7-10 days. If there is no clinical improvement within 48 hours in terms of fever reponse, respiratory rate, or peripheral perfusion, ampicillin or chloramphenicol is replaced by ceftriaxone 100 mg/kg once daily, while gentamicin is continued. Oxygen is provided in case of cyanosis, restlessness, severe chest indrawing, or a respiratory rate >70/minute (27). Specific gastrointestinal infections including cholera, shigellosis and salmonellosis are treated additionally, based upon prevailing antibiotic susceptibility. Nystatin suspension, 100,000 units, is given 6 hourly until thrush is cured, while clotrimazole cream is applied for perianal/vulvovaginal candidiasis.

Vitamin and mineral supplements

Vitamin A for prophylaxis and treatment of xerophthalmia is provided as per WHO recommendations (28). Folic acid, zinc and multivitamins are given for the entire period of stay in the hospital. Folic acid, 1.25 mg, is given once daily, while zinc is given in a dose of 2 mg/kg per day (elemental zinc). Children one year of age and older are supplemented with multivitamin drops 1 mL (containing vitamin A palmitate 5,000 IU, vitamin D 1,000 IU, thiamine hydrochloride 1.6 mg, riboflavin 1 mg, pyridoxine hydrochloride 1 mg, nicotinamide 10 mg, calcium D-pantothenate 5 mg, and ascorbic acid 150 mg) twice daily, half the dose is given to infants less than one year old. Intramuscular magnesium sulfate (50% w/v), 0.4 mmol/kg, is given once daily for 7 days. Iron, 3 mg/kg per day (elemental iron), is started only after the children are stable, afebrile and begin to gain weight, and the treatment is continued for 2 months. Iron supplementation is usually be started in the NRU during the second week of management.

Complications

Hypoglycaemia (blood glucose <3 mmol/L) is managed with 50 mL of 10% glucose administered orally or through a NG tube. If a hypoglycaemic child is unconscious or convulsing, 25% glucose is administered i.v., 2 mL/kg, followed by oral glucose. Children with severe acidosis (serum CO_2 <6 mmol/L) are given sodium bicarbonate 1 mL/kg i.v. slowly. Normal saline or solution A is infused 20 mL/kg over one hour in case of septic shock and the infusion is repeated once if necessary. Children with hypokalemia receive oral potassium, 5 mmol/kg per day. Children with a serum K^+ <2 mmol/L requiring parenteral hydration are infused with an i.v. fluid containing K^+ up to 40 mmol/L. If the haematocrit is <15%, 10 mL/kg of packed red cells or whole blood is transfused over 3 hours. Hypothermia, abdominal distension, congestive heart failure, and weeping skin lesions are managed according to WHO guidelines (18).

Follow up

Upon discharge from the NRU, children are advised to attend the nutritional follow up clinic (NFU) at intervals of one week, two weeks, and then one month until achievement of WL z-score >−1, which is usually possible in 6-8 months. A health worker discusses the overall condition of the child, the change in weight and the child's diet with the mother during each follow-up visit. Intercurrent illnesses are treated. Preparation of khichuri and halwa is demonstrated, health and nutrition education provided to the mothers. Health workers visit the homes of defaulting children.

Outcome variables

The two major outcome variables that will be compared between the study and placebo groups are:

1. Rate of weight gain, calculated from lowest and discharge weights in terms of g/kg body weight per day.
2. Days to achieve edema-free weight-for-length (WL) z-score >−2 according to the US National Centre for Health Statistics reference.

Sample size

An analysis of 66 severely malnourished children (WL <70%) recovering from diarrhea who received nutritional rehabilitation in our NRU showed that their weight gain was 11.4 ± 6.0 g/kg per day, and the time to achieve 80% WL was 15.5 ± 9.4 days. Assuming worthwhile differences of 3 g/kg per day for weight gain and 5 days for time to achieve 80% WL (WL z-score >–2) with metronidazole treatment, sample sizes of 63 and 56 children respectively in each group are calculated using the formula:

$$\frac{2\,(SD)^2}{(WD)^2} \text{ . factor for } \alpha, \beta$$

where, SD is the standard deviation, WD is the worthwhile difference, power is 80%, and type I error is 0.05. Taking the greater of the two calculated sample sizes and allowing for 10% dropouts (refusal to continue, or later diagnosed to have tuberculosis), there will be 70 children in each group.

Facilities Available

Describe the availability of physical facilities at the place where the study will be carried out. For clinical and laboratory-based studies, indicate the provision of hospital and other types of patient's care facilities and adequate laboratory support. Point out the laboratory facilities and major equipments that will be required for the study. For field studies, describe the field area including its size, population, and means of communications. **(TYPE WITHIN THE PROVIDED SPACE).**

Severely malnourished children will be treated for the acute phase of malnutrition in the general ward or special care unit of the CRSC of ICDDR,B. This will follow the routine practice in the CRSC. The children will be transferred to the NRU of the CRSC as soon as the acute phase treatment is complete and the children are fit for the nutritional rehabilitation phase. Treatment will be provided by a team consisting of study investigators and CRSC staff members. Existing diagnostic laboratory and radiology facilities of the Centre will be utilized.

Data Analysis

Describe plans for data analysis. Indicate whether data will be analyzed by the investigators themselves or by other professionals. Specify what statistical softwares packages will be used and if the study is blinded, when the code will be opened. For clinical trials, indicate if interim data analysis will be required to monitor further progress of the study. **(TYPE WITHIN THE PROVIDED SPACE).**

The investigators will perform data entry, data cleaning and analysis themselves. Data will be entered into a personal computer simultaneously with the progress of each subject. SPSS Windows software will be used to analyse data. The software Epi info 6.0 will be used to calculate anthropometric indices. The outcome variables will be compared both within (if applicable) and between groups from enrollment to discharge. For normally distributed quantitative variables, means will be compared by Student's t-test. Variables not normally distributed will be log transformed before analysis. Categorical variables will be compared by Chi-square, multiple or logistic regression will be performed to minimise bias if required.

The code will be opened only after a preliminary analysis has been performed using dummy group names for the study and control groups, provided by the code holder, e.g., groups A and B. If an enrolled child develops a condition requiring metronidazole therapy, i.e., toxic colitis or peritonitis, then his/her code may be opened. Data from all randomized children will be included in the analysis. As all children will be enrolled with an intention to treat, data of children withdrawn from the study but who continue to remain and receive treatment in the hospital will also be included in the analysis.

Ethical Assurance for Protection of Human Rights

Describe in the space provided the justifications for conducting this research in human subjects. If the study needs observations on sick individuals, provide sufficient reasons for using them. Indicate how subject's rights are protected and if there is any benefit or risk to each subject of the study.

The study will test the hypothesis that use of the medicine, metronidazole, will improve the outcome of acute phase treatment and nutritional rehabilitation of severely malnourished children recovering from diarrhea and other acute illness(es). Metronidazole is not a new medication, and its use is expected to eliminate small intestinal bacterial overgrowth as well reduce the morbidity and mortality from life-threatening anaerobic infections in children with severe malnutrition. This study aims at improving the outcome of treatment of severely malnourished children who are brought to the hospital in an acutely ill condition.

The parents will always have the right to withdraw their children from the study at any time. Children so withdrawn will be provided the conventional treatment at the CRSC. Enrolled children, randomized to metronidazole, are expected to benefit from the advantages of better weight gain, lesser duration of stay in the nutrition unit, and lesser morbidity. Enrollment into the study will pose no added risk to a child, other than the inherent risks of severe malnutrition.

Use of Animals

Describe in the space provided the type and species of animal that will be used in the study. Justify with reasons the use of particular animal species in the experiment and the compliance of the animal ethical guidelines for conducting the proposed procedures.

Not applicable

Literature Cited

Identify all cited references to published literature in the text by number in parentheses. List all cited references sequentially as they appear in the text. For unpublished references, provide complete information in the text and do not include them in the list of Literature Cited. There is no page limit for this section, however exercise judgment in assessing the "standard" length.

1. Schofield C, Ashworth A. Why have mortality rates for severe malnutrition remained so high? Bull WHO 1996;74:223-229.

2. Roy SK, Chowdhury AKMA, Rahaman MM. Excess mortality among children discharged from hospital after treatment for diarrhoea in rural Bangladesh. BMJ 1983;287:1097-1099.

3. Ahmed T, Ali M, Ullah M, Choudhury IA, Haque ME, Salam MA, Rabbani GH, Suskind R, Fuchs G. Mortality in severely malnourished children with diarrhea and use of a standardised management protocol. The Lancet (in press).

4. Ahmed T, Adhikary S, Fuchs G, et al. Assessment of a standardized dietary management protocol for the catch-up growth phase of nutritional rehabilitation in very severely malnourished children. ICDDR,B annual report 1997, p. 14.

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16. Rowland MGM, McCollum JPK. Malnutrition and gastroenteritis in the Gambia. Trans Roy Soc Med Hyg 1977;71:199-203.

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18. World Health Organization. Management of the child with severe malnutrition. A manual for physicians and other senior health workers. Geneva, 1999.

19. Hammond GC, Heikens GT, Jackson AA. Small bowel bacterial overgrowth in malnourished children as measured by breath hydrogen test. WI Med J 1985;34:48-49.

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22. Heikens GT, Schofield WN, Dawson S. The Kingston Project. II. The effects of high energy supplement and metronidazole on malnourished children rehabilitated in the community: anthropometry. Eur J Clin Nutr 1993;47:160-173.

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25. Archer GL, Polk RE. Treatment and prophylaxis of bacterial infections. In: Fauci SA, Braunwald E, Isselbacher KJ et al, eds. Harrison's Principles of Internal Medicine, volume 1, 14th edition. New York: McGraw-Hill, 1998; pp 856-69.

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28. World Health Organization. Strategies for the prevention of blindness in national programmes: a primary health care approach. Geneva, 1997.

Dissemination and Use of Findings

Describe explicitly the plans for disseminating the accomplished results. Describe what type of publication is anticipated: working papers, internal (institutional) publication, international publications, international conferences and agencies, workshops etc. Mention if the project is linked to the Government of Bangladesh through a training programme.

The results of this study are expected to be disseminated through local, regional and international scientific conferences. The results will also be published in an international, peer-reviewed journal for wider dissemination. If the treatment with metronidazole is found to be effective, it will be incorporated into the management protocol for severe malnutrition which is an integral component of training programmes organised by the Centre for health professionals seconded by the Government of Bangladesh.

Collaborative Arrangements

Describe briefly if this study involves any scientific, administrative, fiscal, or programmatic arrangements with other national or international organizations or individuals. Indicate the nature and extent of collaboration and include a letter of agreement between the applicant or his/her organization and the collaborating organization. **(DO NOT EXCEED ONE PAGE)**

Nil

Biography of the Investigators

Give biographical data in the following table for key personnel including the Principal Investigator. Use a photocopy of this page for each investigator.

Name	Position	Date of Birth
Dr. Tahmeed Ahmed	Associate Scientist & Coordinator Child Health Programme Clinical Sciences Division, ICDDR,B	November 24, 1959

Academic Qualifications (Begin with baccalaureate or other initial professional education)

Institution and Location	Degree	Year	Field of Study
Mymensingh Medical College, University of Dhaka	MBBS	1983	Medical Science
University of Tsukuba, Japan	PhD	1996	Childhood food allergy

Research and Professional Experience

Concluding with the present position, list, in chronological order, previous positions held, experience, and honours. Indicate current membership on any professional societies or public committees. List, in, chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. **(DO NOT EXCEED TWO PAGES, USE CONTINUATION SHEETS).**

1. In-service training majoring in internal medicine, from December 1983 to December 1984, at Mymensingh Medical College Hospital.
2. Medical Officer (Maternal & Child Health and Family Planning), Rural Health Complex, Ministry of Health, GoB till February 1985.
3. Joined as Medical Officer, Clinical Research Centre, ICDDR,B on February 25, 1985.
4. Worked in Dhaka Children's Hospital as a resident in Pediatrics from August 1989 to August 1990, on deputation from the Centre.
5. Clinical training in the Dept. of Pediatrics, University of Tsukuba Hospital, Japan from October 1990 to March 1992.
6. Promoted to the position of senior medical officer grade II on January 1, 1993.
7. Performing the additional responsibility of coordinator, Child Health Programme, CSD from August, 1996 till date.
8. Promoted to the position of associate scientist on May 1, 1999.

Honours

1. Awarded the "Fellowship for innovative research in developing countries" in 1990 by the International Health Federation, UK.
2. Best paper award in Pediatric Gastroenterology in the annual conference of the Commonwealth Society for Pediatric Gastroenterology and Indian Pediatric Association, 1998.
3. International Health Research Award for 1999, Ambulatory Pediatric Association of USA.

Bibliography

Publications during the past three years

1. Mortality in severely malnourished children with diarrhoea and use of a standardised management protocol. Ahmed T, Ali M, Ullah M, Choudhury I, Haque E, Salam A, Rabbani G, Suskind R, Fuchs G. Lancet 1999;353:1919-22.

2. Humoral immune and clinical responses to food antigens following acute diarrhea in children. Ahmed T, Sumazaki R, Shibasaki M, Nagai Y, Shin K, Fuchs GJ, Takita H. *J Paediatr Child Health* 1998;34:229-232.

3. Circulating antibodies to common food antigens in Japanese children with IDDM. Ahmed T, Komota T, Sumazaki R, Shibasaki M, Hirano T, Takita H. *Diabetes Care* 1997;20:74-76.

4. Immune response to food antigens: Kinetics of food-specific antibodies in the normal population. Ahmed T, Sumazaki R, Shibasaki M, Takita H. *Acta Paediatr Japonica* 1997;39:322-328.

5. Gastrointestinal allergy to food: a review. Ahmed T and Fuchs G. *J Diarrhoeal Dis Res* 1997;15:211-223.

6. Resolution of protein-losing hypertrophic gastropathy by eradication of *Helicobacter pylori*. Yamada S, Sumazaki R, Ahmed T, Takita H. *Eur J Pediatr* 1997;156:182-185.

7. Cow's milk allergy in children: association with IgG and IgE antibodies to milk protein and presentation of a case. Ahmed T, Sumazaki R, Shibasaki M, Takita H. In: Book of programme and abstracts, Sixth Annual Scientific Conference, ICDDR,B, 1997, p58.

8. Standardised management reduces mortality among severely malnourished children with diarrhoea. Ahmed T, Ali M, Ullah M, et al. J Diarrhoeal Dis Res 1998;16:42.

Detailed Budget for New Proposal

Project Title: Use of metronidazole in improving nutritional rehabilitation ...randomized controlled trial

Name of PI: Dr. Tahmeed Ahmed

Protocol Number: Name of Division: CSD

Funding Source: World Bank Amount Funded (direct): $ Total: Overhead (%)

Starting Date: 01.10.2000 Closing Date: 30.9.2002

Personnel		**Rate/mo**	**1st yr**	**2nd yr**	**Total**
Dr. Tahmeed Ahmed (2989-2)	20%	1219	2,926	3,072	5,997
Dr. M. Jahangir Hossain (5789-3)	10%	705	846	888	1,734
Medical Officer (NOA/S-1/CSA	100%	635	7,620	8,001	15,621
Health Assistant (GS-3/S-1/CSA) x 2	100%	224	5,376	5,645	11,021
Health Workers (CSA) x 4	100%	60	2,880	3,024	5,904
Secretarial service (Patwary, 2651-8)	10%	643	772	810	1,582
Sub-total:			**20,419**	**21,440**	**41,859**
International Travel (for presentation of study			-	3000	3,000
results in international seminar/conference)					
Sub-total:			**(3,000)**	**3000**	**3,000**
Supplies and Materials					
Medicine			150	100	250
Hospital supplies			50	50	100
Office stationery			200	100	300
Non-stock supplies			300	300	600
Sub-total:			**700**	**550**	**1,250**
Interdepartmental services					
Local transport			100	100	200
Photocopying			50	50	100
Medical illustration			100	100	200
Library service			50	50	100
Sub-total:			**300**	**300**	**600**
Other contractual services					
Postage, fax, DHL			100	100	200
Priting & publication			-	300	300
Sub-total:			**100**	**400**	**500**
Direct cost			**21,519**	**25,690**	**47,209**

Budget Justifications

Please provide one page statement justifying the budgeted amount for each major item. Justify use of man power, major equipment, and laboratory services.

Manpower

Dr. Tahmeed Ahmed:	Responsible for protocol development, fund procurement, supervision of project staff, provision of care to the patients, data management and analysis. This will involve 25% of the PI's time.
Dr. A.M. Khan:	5% of the investigator's total efforts will be directed to ensuring quality of patient care and supervision of project staff.
Dr. Md. Jahangir Hossain:	10% salary of the investigator's efforts will be directed to ensuring quality of patient care as well as data analysis.
Dr. Munirul Islam:	Responsible for subject enrollment and provision of care.
Dr. Baitun Nahar:	Responsible for subject enrollment and provision of care.
Dr. George Fuchs:	Helped the PI in development of the protocol. Will advise on data management, analysis, and manuscript preparation.
Medical Officer:	Responsible for enrollment and management of patients. Will also supervise project staff. Data entry, data cleaning and analysis will also be performed by the incumbent, on a 100% effort basis.
Health Assistants:	Will assist in subject enrollment, provision of care and follow-up. These works will require 100% efforts.
Health Workers:	Will provide ancillary support to the care of children while they stay in the hospital, and help the health assistants during follow-up.

Supplies & interdepartmental services

The children will require medicines and diagnostic tests whenever they have any inter-current illness. The budget for medicines and interdepartmental services including use of diagnostic facilities is justified in view of the high morbidity among severely malnourished children.

Utilities and transport

Children will be visited at home if they fail to attend the follow-up clinic. These visits will involve transport fare.

International travel

This will cover travel and per diem costs for travel abroad for dissemination of study results.

Appendix: Composition of Liquid Diets

	Milk suji	Milk suji 100
Whole milk powder (g)	40	80
Rice powder (g)	40	50
Sugar (g)	25	50
Soya oil (g)	25	25
Egg albumin (g)	-	-
$MgCl_2$ (g)	0.5	0.5
KCl (g)	1.0	1.0
Calcium lactate (g)	2.0	2.0
Cooked volume (L)	1.0	1.0
Energy (kcal/100 mL)	67	100
Protein (g/100 mL)	1.4	2.6
PER %	8	10
FER %	47	40

Appendix: Composition and Preparation of Halwa

Ingredient	Amount	Energy (kcal)	Protein (g)
Wheat flour (atta)	200 g	682	24
Lentils (mashur dal)	100 g	343	26
Oil (soya)	100 ml	900	-
Molasses (brown sugar or gur)	125 g	479	0.5
Water	600 ml (to make a thick paste)	-	-
Total weight of halwa	1,000 g	-	-
Total energy and protein per kg	-	2,404	50.5

100 g of cooked halwa contains 240 kcal and 5 g protein.
1 cup (130 g) of cooked halwa contains 312 kcal and 6.5 g protein.

The dal is soaked in water for 30 minutes and then crushed. Atta is fried on a hot pan for a few minutes. The atta, crushed dal and oil are mixed with water. Gur is melted and added to the mixture to make a thick halwa.

Appendix: Composition and Preparation of Khichuri

Ingredient	Amount	Energy (kcal)	Protein (g)
Rice	120 g	415	8
Lentils (mashur dal)	60 g	206	15.6
Oil (soya)	70 ml	630	-
Potato	100 g	97	1.6
Pumpkin	100 g	25	1.4
Leafy vegetable (shak)	80 g	22	2
Onion (2 medium size)	50 g	25	-
Spices *	50 g	22	1
Water	1,000 ml	-	-
Total weight of khichuri	1,000 g	-	-
Total energy and protein per kg	-	1,442	29.6

* Spices include ginger, garlic, turmeric and coriander powder.
100 g of cooked khichuri contains 145 kcal and 3 g protein.
1 cup (130 g) of cooked khichuri contains 190 kcal and 4 g protein.

Rice, dal, oil, spices and water are added to a pot and boiled. After about 20 minutes, the potatoes and pumpkin cut into pieces, and spices are added. Just 5 minutes before the rice is cooked, cleaned and chopped leafy vegetable is added. The pot is kept covered during cooking. Khichuri takes about 50 minutes to cook.